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Research paper

White matter volumes in youth offspring of bipolar parents

Fabiano G. Nery[a,*], Matthew Norris[a], James C. Eliassen[a], Wade A. Weber[a], Thomas J. Blom[a], Jeffrey A. Welge[a], Drew A. Barzman[a,b], Jeffrey R. Strawn[a], Caleb M. Adler[a], Stephen M. Strakowski[a], Melissa P. DelBello[a]

[a] Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, OH, USA
[b] Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

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ABSTRACT

Background: Studying youth at high risk of developing bipolar disorder may clarify neurobiological factors associated with vulnerability to this illness. We present here a baseline characterization of brain structure in youth at-risk for bipolar disorder.

Methods: Magnetic resonance images were obtained from 115 child and adolescent offspring of bipolar disorder type I subjects and 57 healthy child and adolescent offspring of healthy parents (healthy control offspring). Offspring of parents with bipolar disorder were divided into healthy bipolar offspring (n=47) or symptomatic bipolar offspring (n=68), according to presence or absence of childhood-onset psychopathology. All bipolar offspring were free of major mood and psychotic disorders. Gray (GM) and white matter (WM) volumes were compared between groups using voxel-based morphometry.

Results: No differences in GM volumes were found across groups. Healthy bipolar offspring presented with decreased WM volumes in areas of the right frontal, temporal and parietal lobes, and in the left temporal and parietal lobes compared to healthy control offspring. Symptomatic bipolar offspring did not present with any differences in WM volumes compared to either healthy bipolar offspring or healthy control offspring.

Limitations: Cross-sectional design and heterogeneous sample of symptomatic bipolar offspring.

Conclusions: WM volume decreases in areas of the frontal, occipital, and parietal lobes are present in bipolar offspring prior to the development of any psychiatric symptoms, and may be a correlate of familial risk to bipolar disorder. In this large cohort, we have not found evidence for regional GM volume abnormalities as an endophenotype for bipolar disorder.

1. Introduction

Bipolar disorder is highly heritable. Children of parents with bipolar disorder are at increased risk of developing mood disorders in general, and bipolar disorder in particular (DelBello and Geller, 2001; Birmaher et al., 2009; Gottesman et al., 2010; Duffy et al., 2014). When both parents have bipolar disorder, the risk of developing this illness among their offspring more than doubles when compared with the risk in offspring of one affected parent (Birmaher et al., 2009; Gottesman et al., 2010). The first symptoms of bipolar disorder often emerge during adolescence (DelBello and Geller, 2001; Birmaher et al., 2009; Gottesman et al., 2010; Duffy et al., 2014; Reichart et al., 2005). Prospective and retrospective studies suggest that early psychopathology, particularly childhood anxiety disorders, mood symptoms, and externalizing disorders, predicts later development of major mood disorders in offpspring of bipolar parents (Duffy et al., 2014; Henin et al., 2005; Goldstein et al., 2010; Nurnberger et al., 2011; Duffy et al., 2013). The neurobiological mechanisms of disease associated with the development and progression of these early symptoms – prior to a syndromic mood episode – in youth at risk for bipolar disorder are unknown. Thus, studies of adolescents and young adults at familial risk for developing bipolar disorder may identify neurobiological correlates of familial risk and of early psychopathology, which could inform both early detection and intervention strategies (DelBello and Geller, 2001).

Bipolar disorder is characterized by dysfunction of affect regulation and attentional processes (Goodwin and Jamison, 2007). Structural, neurochemical, and functional abnormalities within emotional control networks that include the ventrolateral and ventromedial prefrontal cortices, thalamus, amygdala, and striatum might underlie the dysfunctional affect and cognitive processes seen in bipolar disorder (Strakowski et al., 2005, 2012). Prior to developing mood disorders, youth bipolar offspring present with difficulties in tasks of executive

* Correspondence to: Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, 260 Stetson St, Suite 3200, Cincinnati, OH 25221, USA.
E-mail address: neryfo@ucmail.uc.edu (F.G. Nery).

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functioning, memory, and attention, suggesting that a pre-existent fronto-limbic dysfunction may contribute to the development of mood disorders in those youth at familial risk (Schneider et al., 2012; Meyer et al., 2004; Gotlib et al., 2005; Ladouceur et al., 2013).

Imaging studies of neuroanatomical substrates that could reflect these observed functional abnormalities in bipolar offspring have yielded inconclusive results (Schneider et al., 2012; Nery et al., 2013). Several studies using either region-of-interest or voxelwise approaches found no structural gray matter (GM) abnormalities in youth bipolar offspring (Hajek et al., 2008a, 2008b, 2009, 2010; Singh et al., 2008; Takahashi et al., 2010; Sugranyes et al., 2015). Relatively few studies found increased GM volumes in right inferior frontal gyrus (Hajek et al., 2013), left parahippocampal gyrus (Ladouceur et al., 2008), and amygdala (Bauer et al., 2014) in youth bipolar offspring compared with offspring of healthy parents. Other controlled studies found decreased GM volumes in the right orbitofrontal, middle frontal, bilateral superior, and middle temporal cortices (Hanford et al., 2016a), and decreased cortical thinning in portions of the temporal and middle frontal regions (Hanford et al., 2016b) in youth bipolar offspring. In contrast, findings of WM abnormalities in either adults or youth at-risk for bipolar disorder have been more consistent (Kieseppa et al., 2003; McDonald et al., 2004; Matsuo et al., 2012; Hulshoff Pol et al., 2012; Sprooten et al., 2011, 2013; Skudlarski et al., 2013; Mahon et al., 2013; Frazier et al., 2007; Roybal et al., 2015; Teixeira et al., 2014; Versace et al., 2010). Specifically in youth, abnormal fractional anisotropy, a measure of WM integrity, in the bilateral longitudinal fasciculi (Frazier et al., 2007), cingulum, cingulate, corpus callosum, and superior and inferior fasciculi (Roybal et al., 2015) has been described in bipolar offspring compared with youth with healthy parents. To the best of our knowledge, no study has investigated WM volumes in youth bipolar offspring.

The relative preponderance of findings of WM abnormalities versus GM abnormalities in bipolar offspring is still difficult to interpret. It might reflect several different factors such as choice of imaging techniques, sample size and statistical power, variability in age and brain development between adult versus child offspring, as well as degrees of comorbid psychopathology among the study populations. An alternative hypothesis is that in bipolar disorder, WM abnormalities prior to illness onset reflect genetic risk, given the consistency of findings among bipolar offspring; in contrast, as GM changes are less frequently reported prior to illness onset, they may represent effects of emerging psychopathology, illness burden, or medication exposure (Schneider et al., 2012; Nery et al., 2013). Recent evidence suggest that even unaffected bipolar offspring present with GM abnormalities that might be markers of illness vulnerability (Bauer et al., 2014; Hanford et al., 2016b). Therefore, a study that examines brain structural differences in adolescent bipolar offspring attempting to differentiate effects of familial risk versus effects of early psychopathology might help to further investigate this assumption.

With these considerations in mind, we examined GM and WM volumes in a large sample of children and adolescents at-risk of developing bipolar disorder. We sought to investigate the effects of familial risk and psychopathology in a cohort that was large enough to facilitate within-group comparisons. We hypothesized that: 1) GM volume abnormalities in ventral prefrontal emotional control networks would be associated with early psychopathology in youth at increased familial risk for bipolar disorder; and 2) WM volume abnormalities in ventral prefrontal emotional control networks would be associated with increased familial risk for bipolar disorder.

2. Methods

This report is a baseline analysis of an ongoing prospective study to characterize neurodevelopmental changes in children and adolescents at-risk for bipolar disorder. The sample was comprised of offspring of bipolar disorder parents ("bipolar offspring," n=115), and offspring of healthy parents ("healthy control offspring," n=57). Participants were recruited from the local community through posted flyers and word of mouth. After study procedures were explained, participants (if >18 years old), or parents or legal guardians gave written informed consent and youth gave written assent (if <18 years old) to participate in the study. The University of Cincinnati Institutional Review Board approved all procedures related to this study.

Inclusion criteria for bipolar offspring were ages between 9 and 20 years, having at least one biological parent with bipolar disorder type I, and no DSM-IV-TR major mood or psychotic disorder in themselves (including bipolar disorder types I, or II, cyclothymic disorder, dysthymia, major depressive disorder, schizophrenia, schizoaffective disorder or psychotic disorder not otherwise specified). Inclusion criteria for healthy offspring were age between 9 and 20 years, no personal history of any Axis I psychiatric disorder, and no first-degree relatives with any history of mood or psychotic disorders. Exclusion criteria for both groups were any history of alcohol or drug dependence, or any alcohol or drug abuse within the previous 3 months, any medical or neurological disorder that could influence results, IQ lower than 70, any contraindication to MRI scan (*e.g.*, braces, metallic implants), and any history of head trauma with loss of consciousness more than 10 min. Subjects had to be medication-free at time of participation in the study, with the exception of stimulant treatment for ADHD. Subjects on stimulants were asked to hold on taking those medications for 48 h before the scan.

In offspring, psychiatric diagnoses were determined using the *Kiddie-Schedule for Affective Disorders and Schizophrenia Lifetime Version* (K-SADS-PL) (Kaufman et al., 1997) and the Mood Disorders section of the Washington University at St. Louis Kiddie-Schedule for Affective Disorders and Schizophrenia WASH-U KSADS (Geller et al., 2001). The K-SADS-PL is a semi-structured interview that integrates parent and child information to obtain current and lifetime childhood-onset psychiatric diagnoses according to DSM-IV, and has good to excellent concurrent validity and inter-rater reliability (Kaufman et al., 1997). The WASH-U KSADS Mood Disorders section is a module developed to expand the examination of onset and offset of mood episodes, and has good reliability (Geller et al., 2001). In parents, psychiatric diagnoses were determined using the Structured Clinical Interview for Diagnosis (SCID) (DSM-IV) (First et al., 2002). The SCID is a structured modular interview to diagnose current and lifetime psychiatric diagnoses according to DSM-IV criteria (First et al., 2002). A Masters-level trained clinician or board-certified psychiatrist performed these diagnostic interviews. Diagnoses were validated in best estimate meetings attended by at least three board-certified psychiatrists or child psychiatrists or psychologists. Current mood symptoms were evaluated using the Hamilton Depression Rating Scale (HAMD) 17-items for depressive symptoms (Hamilton, 1976) and the Young Mania Rating Scale (YMRS) for manic symptoms (Young et al., 1978). The HAMD-17 is a widely used scale to rate the severity of depressive symptoms occurring in the 7 days prior to the interview. It has been shown to have adequate validity and reliability in the age range of our sample (Patel et al., 2006). The YMRS is a widely used rating scale to assess presence of manic symptoms in the 7 days prior to the interview, and has been shown to valid and reliable for use in child and adolescent samples (Youngstrom et al., 2002).

We divided the bipolar offspring in two subgroups according to the presence or absence of lifetime psychopathology (hereafter called symptomatic bipolar offspring (n=68) and healthy bipolar offspring (n=47), respectively). The symptomatic bipolar offspring included youth with definite psychiatric disorders and/or with subthreshold psychiatric symptoms with obvious impairment from those symptoms, and the healthy bipolar offspring included youth with no psychiatric symptoms or with few symptoms and no impairment from those symptoms. The majority of subjects that met criteria for lifetime psychopathology also met criteria for current psychopathology, except 2 subjects with depressive disorder NOS, and 1 subject with general-